MEDICAL PROGRESS:

Recent Progress In The Treatment Of Thrombo-Embolic Disease

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INTEREST in the problems of venous thrombosis and pulmonary embolism has increased rapidly during the past decade. This interest has been stimulated to a great extent by the controversy which has arisen as to the best method of prevention and treatment. The heat of controversy has fortunately been accompanied by considerable light shed upon the fundamental problems involved. Equally fortunate for patients suffering from these conditions is the fact that these new therapeutic measures have all brought great reductions in morbidity and mortality in comparison with the results obtained by the time-honored expectant treatment of rest, elevation and the application of heat.

Primary consideration in the treatment of thrombo-embolic disease should necessarily be given to reducing the mortality from pulmonary embolism. Of importance also are efforts to decrease the morbidity from thrombosis and the disabilities arising from thrombophlebitis.

INCIDENCE

Consideration of the incidence of thrombosis and pulmonary embolism serves to call attention to the conditions under which these complications are likely to arise. The percentage of cases of thrombo-embolism encountered in the course of routine hospitalization is small. In 172,888 records of surgical patients at the Mayo Clinic[6] only 0.96 per cent suffered this complication. The incidence in 125.524 postoperative cases reported by Zilliacus[50] was 0.51 per cent. In selected groups of patients, however, such as those subjected to extensive abdominal operations for cancer, abdominal hysterectomies, prostatectomies and operations on the biliary tract the number of cases increases considerably. Crafoord and Jorpes[16] report a 9 per cent incidence of thrombo-embolism in 1,111 cases of this nature. Murray and Best[36] have shown a similar high incidence in patients operated on at the Toronto General Hospital. Pulmonary embolism has been found to be the most common cause of death after fractures of the hip by Golodner, Morse and Angrist.[24] The increased incidence of pulmonary embolism in obese patients first pointed out by Snell[45] has been emphasized by Ochsner.[38]

When careful search for antemortem thrombosis has been made in the course of postmortem examinations in an unselected group of cases, an astonishingly high incidence of intravascular thrombosis has been found. Rössle[42] found that the veins of the calf harbored thrombi in 27.1 per cent of 324 patients over 20 years of age. In their first report, Hunter[30] and his colleagues found thrombosis of the deep veins of the leg in 52.7 per cent among 351 middle-aged and older persons forced to bed for varying periods of time. Pulmonary embolism, however, was the cause of death in only 3.13 per cent of the deaths. It is highly probable that intravascular thrombosis occurs far more frequently than it is recognized and that many cases subside spontaneously without complications.

Analysis of the cases of fatal pulmonary embolism with respect to the clinical condition from which the patient was originally suffering calls attention to the wide field in which the problem of thrombo-embolism is present. Only 40 per cent of the 370 cases studied by Hampton and Castleman[25] followed operation. Cardiac disease was a predisposing factor in 30 per cent and patients suffering from general medical conditions accounted for the remaining 30 per cent. As Hunter[31] has remarked, "The greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person."

Whereas the incidence of thrombo-embolism is relatively low in the general run of clinical conditions, once intravascular thrombosis has occurred, as manifested by thrombophlebitis, phlebothrombosis or pulmonary infarction, the frequency of subsequent pulmonary embolism is alarmingly high. In 897 cases of thrombophlebitis reported from the Mayo Clinic by Allen, Barker and Hines,[4] subsequent pulmonary embolism occurred in 15.6 per cent and the embolus was fatal in 5.7 per cent. In 678 patients who survived an initial pulmonary embolus, subsequent embolism took place in 30.5 per cent and in 18.3 per cent fatal pulmonary embolism occurred. Bauer[9] over a ten-year period observed a mortality from pulmonary embolism of 18 per cent in 264 cases of thrombosis. The significance of these findings was emphasized by Barker[6] and his co-workers: "If all fatal embolisms which were preceded by a clinically diagnosed nonfatal embolism could be prevented, the total number of fatal embolisms would be reduced by more than a third." If, in addition, all the clinically recognizable cases of thrombosis could be satisfactorily treated, the incidence of fatal pulmonary

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embolism might be reduced to a considerable degree.

Two problems in diagnosis arise in thrombo-embolism, that of intravascular thrombosis and that of pulmonary embolism.

Thrombosis. The location of the intravascular thrombosis in the great majority of cases has been in the lower extremities. From combined clinical diagnosis and incidental necropsy findings 96.8 per cent of the cases were found by Allen, Barker and Hines[4] to involve the veins of the lower extremities. Bauer[9] believes that the origin of the thrombosis in thrombo-embolic disease is in the lower extremities in 98 per cent of the cases. Early diagnosis of thrombosis in the veins of the leg is therefore to be sought. It is important at this time to emphasize the difference in the clinical picture presented by thrombosis occluding the femoral and iliac veins, the so-called phlegmasia alba dolens, with its readily recognizable swelling, pain and fever, and the more insidious thrombosis originating in the veins of the foot or calf. This latter condition Homans[27] has termed "deep quiet venous thrombosis" while Ochsner and DeBakey[39] have identified it as "phlebothrombosis." Bauer[9] prefers the designation "acute thrombosis of the deep veins." Distinction between the two conditions is important since the bland thrombosis starting in the leg frequently gives no signs or symptoms of its presence until pulmonary embolism occurs. The first indication of venous thrombosis in 41 per cent of the 202 cases reviewed by Allen, Linton and Donaldson[1] was pain in the chest. Of greater significance in the early diagnosis of thrombo-embolic disease in their patients was an unexplained simultaneous elevation of the temperature, pulse and respiration on the clinical chart. This sign was the first one noted in 81 per cent of their series. Careful examination of the legs in all patients in the older age group who are confined to bed should be a routine daily practice. Tenderness over the calf, increased warmth of the skin over the calf or foot and pain or restriction of motion on dorsiflexion of the foot, which Homans[28] calls the "dorsiflexion sign," may indicate early thrombosis in the deep veins of the leg. Observation of the difference in the rate of drainage of blood from the soles of the feet upon moderate elevation has, in my experience, been useful in detecting early changes in the efficacy of venous outflow. A method of differentiating the tenderness due to thrombosis of the veins of the calf from tenderness of the muscles due to other causes was suggested by Moses.[34] He first examines the deep structures of the calf by pressure with the tips of the fingers. Tenderness elicited by this procedure is then compared with that produced by lateral pressure on the calf muscles. Phlebography, once advocated for the early diagnosis of deep thrombosis of the leg, has not been found a reliable means for establishing the diagnosis in the hands of most observers. Phlebograms are difficult to interpret and spasm of the larger veins, which has clearly been demonstrated by Papper and Imber,[41] may be misleading. Bauer,[10] on the other hand, has developed a standard technique whereby the deep veins of the leg, particularly the peroneal veins, are filled by a slow injection of contrast medium into the short saphenous system. The vein is exposed by a small incision behind the lateral maleolus and the needle temporarily tied in place. Films are taken in two planes at 50 and 60 seconds during the injections. His studies on the pathogenesis of thrombosis of the deep veins of the leg have been an outstanding recent contribution.

Pulmonary Embolus. Since pulmonary embolism is frequently the first clinical evidence of intravascular thrombosis, early diagnosis of this condition is urgent in order to prevent recurrence. The classical picture of sudden pain in the chest, dyspnea and hemoptysis is by no means universal. Nor is it necessary for the patient to have been confined to bed. Homans[28] was the first to call attention to the development of pulmonary infarction in apparently healthy adults. Careful examination was necessary in order to disclose the site in the legs from which the emboli arose. Hampton, Prandoni and King[26] have reported ten cases of pulmonary embolism from obscure sources. The patients were all healthy adults who were admitted to the hospital for acute pulmonary conditions. The diagnosis of pulmonary infarction was made on the basis of x-ray examination of the chest, electrocardiogram and phlebography. Except in one of the cases, there was no obvious sign of venous thrombosis. Recovery took place in all patients following treatment with anticoagulants. The x-ray diagnosis of pulmonary infarction has been carefully investigated by Hampton and Castleman,[25] both in the living patient and at autopsy. The site of lodgement of the embolus was in the lower lobes in 74 per cent of their cases with slight preferment for the lower lobe on the right side. They have stressed the fact that the area of infarct is always in contact with one of the pleural surfaces and that the border towards the heart when viewed from the correct angle always presents a peculiar "hump." Embolism need not produce infarction. In a number of their cases spontaneous resolution occurred. To this process they have given the term "incomplete infarction." Because of the changing appearance over a short space of time they advocate repeated examinations in cases who are suspected of having suffered a pulmonary embolus. Repeated electrocardiographic examinations are indicated in the doubtful cases for the same reason.

ETIOLOGY AND PREVENTION

Three etiological factors responsible for thrombosis have been emphasized by deTakats and Fowler,[18] slowing of the circulation, changes in the vessel wall and increased coagulability of the blood. Methods of prevention will be considered in the light of these etiological factors.

Slowing of the circulation. Since it is recognized that confinement to bed of a previously ambulatory older person is the most important

predisposing factor in thrombosis, active exercise, especially of the legs, is strongly advocated. Hunter[31] and his associates found that the incidence of thrombosis noted at postmortem examination was reduced to one-third by the institution in the medical department of exercises for the patients. Shaw and Richards[44] found that post-operative embolism was reduced to one-fifth by the institution of regular exercise periods. The importance of supervised exercise in the postoperative period was stressed by Ochsner.[38] At the times that the patient is having his pulse and temperature taken by the nurse he should routinely raise and extend his feet at the ankle. The tight sheets of the neat hospital bed, though esthetically satisfying, facilitate the development of thrombosis by extending the feet and thus producing maximal relaxation of the flexor muscles of the calf. With the patient on his side, however, active movements of the lower extremities can be readily carried out without the production of pain. Even in case that the patient's leg is enclosed in a plaster cast, he can still obtain the advantage of muscular activity by alternately contracting and relaxing his muscles. Bauer[11] has urged this form of exercise, which is particularly important after injuries of the lower extremities, since he has shown that the incidence of thrombosis is in these cases as high as 12 per cent.

It was hoped that "early ambulation" in the postoperative period would bring about a decrease in the incidence of thrombo-embolism. As this procedure is not frequently being carried out, these hopes have not been realized. In fact Blodgett and Beatty[12] have shown that the incidence of thrombo-embolism may actually be increased. Since it is the actual movement which appears to have a beneficial effect and since simply sitting in a chair by the bedside promotes stasis in the veins of the leg it would appear to be a better policy to have the patient get out of bed, walk about a short time and get in again. Once the patient is fully ambulatory and can walk to and fro, the need for supervised exercise is past.

Other measures designed to improve the circulation have been advocated by numerous observers. The importance of elevating the foot of the bed to prevent venous stasis has been repeatedly stressed. Application of pressure to the legs by means of compression bandages in all patients over the age of 45 who undergo an extensive operative procedure has been advocated by Ochsner.[38] It is a logical form of prevention since compression will empty the veins in which blood is not flowing and will speed-up the flow of blood in veins which are carrying the blood to the heart. This compression treatment, which was first advocated by Fischer[23] is especially useful for acute thrombophlebitis. Rapid subsidence of the inflammatory process is facilitated. The exact means by which compression favors resolution is obscure but it may depend upon improving the distribution of blood flow to the peripheral tissues. Chapman and Linton[15] have suggested an explanation of the mechanism by which emboli are broken off to be carried to the lungs during activities associated with straining movements on the part of the patient with the glottis closed. They believe that forceful expiration under these conditions, the so-called Valsalva experiment, causes a sudden backing up of the venus stream with ballooning out of the great veins of the lower half of the body. With the subsequent sudden release of pressure associated with inspiration, the venous pressure falls sharply and if there is a poorly organized thrombus floating in one of the larger veins it may become detached or a part may be broken off during these abrupt changes in venous pressure.

Another factor which is probably of significance in the retardation of the circulation is reflex vasoconstriction due either to temperature changes or to the traumatic stimuli associated with the illness or operative procedure. The increased incidence of thrombo-embolism during the winter months has been noted by Allen, Linton and Donaldson.[2] Naide and Säyen[37] have found that the proportion of patients who had previously developed thrombophlebitis who exhibited an abnormally high vascular tone was greatly in excess of normal. It is likely that vasoconstriction which affects the veins as well as the arteries may be of real signifiance in promoting vascular stagnation.

Endothelial damage. Thrombosis is naturally favored by damage to the intima of vessels though efforts to relate this fact to clinical conditions have been disappointing. Jensen[32] has demonstrated pathological changes in the walls of veins at a level considerably above the region where thrombosis has occurred. Attempts by Tannenberg[46] to produce thrombosis from allergic reactions in the walls of veins by the administration of bacterial toxins in sensitized animals were unsuccessful. Gross trauma to veins will produce thrombosis and this thrombosis can be prevented by regional or general heparinization as shown by Murray and Best,[36] but the importance of this factor in initiating clinical thrombosis is not yet clear. It seems likely that the high incidence of thrombosis in the leg after trauma noted by Bauer[11] is dependent upon direct injury to the vessels.

Increased coagulability of the blood. Increased coagulability of the blood following trauma and operations has long been recognized. Wright[49] has recently demonstrated not only an increase in the number of platelets in the circulating blood after operations or child-birth but also an increase in the adhesive quality of the platelets. Anticoagulants reduce the adhesiveness of the platelets. An increase in the concentration or activity of prothrombin has been demonstrated by Brambel and Loker.[13] They found that by using plasma diluted to 12.5 per cent they were able to demonstrate finer variations in the prothrombin time in the blood. Significant increases were observed after operations and after delivery. Of particular significance were their findings of increased prothrombin activity in cases of phlebitis and after stopping the administration of dicou-

marol. Shapiro[43] suggested the use of this test in differentiating pulmonary embolism from other conditions. He advocated its use in the selection of cases in whom thrombo-embolism was likely to occur. Increased tolerance to heparin following operations was first noticed by Crafoord and Jorpes[16] when they began to use this substance prophylactically in surgical patients. The heparin tolerance test to select patients who might be subject to thrombo-embolism was suggested by deTakats.[19] According to this test the clotting time is measured with a capillary tube 10, 20 and 30 minutes after the intravenous injection of 10 mgm. of heparin. The heparin tolerance was found to increase for the first 3 to 4 days after operation.

Comment. Although recent reports on altered coagulability of the blood as a predisposing factor in the origin of thrombo-embolism are highly suggestive, they do not yet offer much help from the standpoint of prevention. The laboratory determinations are difficult and require highly trained technical assistance. Although the observations are extremely interesting and important for an understanding of the pathogenesis of thrombo-embolism no laboratory test has yet been devised by means of which the individual who will develop intravascular thrombosis can surely be identified.

PROPHYLACTIC TREATMENT

Over the question of the best method of prophylactic treatment of thrombo-embolism the controversy has been the most active. Since both vein ligation and the use of anticoagulants have yielded excellent results in reducing the mortality from pulmonary embolism the advocates of each method have vigorously insisted upon the advantage of their method. Enough time and a sufficient number of cases have now accumulated so that an appraisal can be made.

Vein ligation. All who have had the unhappy experience of watching a thrombosis of the calf ascend and even terminate with a fatal pulmonary embolus cannot help but be impressed with the dramatic results which follow ligation of the vein ahead of the propagating thrombus. Similarly, in the patient who is desperately ill after repeated sub-lethal pulmonary infarcts, the rapid improvement when the vein through which these emboli pass is safely tied off, marks this procedure as a life-saving measure. Allen[3] has recently summarized the results of interruption of the femoral veins in 816 patients at the Massachusetts General Hospital. There was but one death from massive pulmonary embolus following this procedure. Because of the high incidence of involvement of the veins of both legs, bilateral ligation was practiced with rare exceptions. In the last year for which statistics were available 98.2 per cent of the ligations were bilateral. This procedure was used for prophylactic purposes in an increasing number of cases, so that in 1945 over one-third of the ligations were performed for this reason. The indications for ligation in the remaining cases were approximately equally divided between pulmonary embolism and venous thrombosis in the legs. Numerous reports have come out on ligations of the veins at higher levels, common femoral (Fine and Starr[22]), iliac (Bancroft,[5] and Homans[27]) and vena cava (Veal and Hussey,[47] O'Neil[40] and Moses[35]). Although there may be occasional instances in which ligations at these higher levels are indicated, the very fact that anticoagulants have had to be used[5,20] after these high ligations in order to prevent further thrombosis and embolism casts doubt on the necessity and the advisability of such radical procedures. Although ligation of the superficial femoral vein distal to the profunda is seldom followed by signs of venous impairment, ligation of the common femoral vein may have disastrous results. Dennis[17] has reported such a case and Homans[29] states that he has encountered two similar ones. deTakats and Fowler[18] find that ligation of the femoral vein above the profunda invariably results in considerable edema. Although ligation of the common iliac vein and even of the vena cava may allow for a better development of collateral circulation, and Veal and Hussey[47] have commented on the remarkable restoration of function which occurs after ligation of the vena cava, yet accurate studies show the degree of venous insufficiency which follows interruption of the veins at such high levels. Burch and Winsor[14] studied the venous pressure in the feet of five patients in whom the inferior vena cava was ligated for septic phlebitis. All but one of the patients showed edema up to ten months after operation and the venous pressure in all cases was considerably increased with diminution in the digital oscillations. They found, however, that there had been remarkable compensation. Allen,[3] in summarizing the experience with vein ligation at the Massachusetts General Hospital, has concluded that "common femoral vein interruption is not recommended in spite of one fatal embolus from the profunda femoris vein after superficial femoral interruption. Serious sequelae can occur under certain circumstances from common femoral vein occlusion. The technical difficulties far outweigh any added protection to the patient."

Comment. Vein ligation has a very significant place in the treatment of thrombo-embolism. It is especially called for in patients who have had a warning emoblus and in whom careful examination reveals signs of thrombosis in the leg. Under such circumstances both superficial femoral veins should be ligated. Again, evidence of thrombosis in the leg in a patient who for some reason cannot be mobilized calls for bilateral superficial femoral vein ligation. Finally, in cases that the use of anticoagulants is contraindicated, vein ligation may be a life-saving measure. Because of the high incidence of embolism after vein ligation in case that the thrombosis has extended above the superficial femoral vein, there appear to be few indications for ligation above this level.

ANTICOAGULANTS

Heparin. Many favorable reports on the use of anticoagulants for the prophylaxis and treatment of thrombo-embolism have been published. With the use of heparin by continuous intravenous drip, Murray and Best[36] in 1938 reported the successful prophylactic treatment of 315 surgical cases without a single case of thrombo-embolism. Furthermore, in seven cases of pulmonary embolism and 28 cases of thrombophlebitis there was no recurrence. Crafoord and Jorpes[16] in 1941 presented the results they had obtained by the use of heparin given in repeated intravenous injections four times daily. The incidence of thrombo-embolism in over 1,000 cases in the control series was 9 per cent. With the use of heparin in 325 cases there was not a single instance. Bauer[9] has recently summarized his experiences with the administration of heparin in the treatment of thrombosis and embolism over a five-year period. Before the use of heparin, in 264 cases in which the diagnosis of thrombosis had been made, there were 47 deaths, a mortality of 18 per cent. During the five years, with the use of heparin, the diagnosis of venous thrombosis was made and generally confirmed by phlebography in 209 cases. There were but three deaths, a mortality of 1.4 per cent. Only one of these patients was under the influence of heparin at the time of the fatal embolism. Bauer[9] has outlined a plan for the treatment of thrombo-embolism which is commendable for its efficacy and simplicity. The general principles of this plan are essentially (1) early diagnosis, (2) immediate heparinization, (3) active exercises of the legs from the beginning, and (4) early mobilization during the period of heparinization, with a tapering off of the administration of the drug. An initial dose of 150 mgm. of heparin is injected intravenously as soon as the diagnosis is made, followed by one or two more similar doses the first day, depending upon the time of day in which the treatment is started, but never at closer intervals than four hours. On subsequent days the patient is generally given 150 mgm. at night and in the morning, with 100 mgm. at midday. In the mild case this active heparinization is continued for but three to five days and the dosage is then tapered off by omitting one or more doses each day. In the presence of massive pulmonary embolism or extensive thrombophlebitis larger doses of heparin are required. If the patient is not ambulatory the treatment is carried on for a longer period of time. Bauer[9] has emphasized the fact that recurrence of the thrombosis and embolism is apt to occur if the drug is withdrawn too suddenly, and he has strongly advocated the early mobilization of the patient while under the influence of the anticoagulant. Not only was the incidence of pulmonary emoblism reduced to low levels by this form of therapy but the process of thrombosis was definitely arrested. In case that the venous system of the lower leg alone was involved at the time treatment was started and the process arrested at this point, the development of collateral venous circulation was most satisfactory and the resultant post-phlebitic difficulties minimal. In case that the femoral vein was already involved at the time the anticoagulant was started, some disability generally resulted. Early treatment with heparin not only lowered the mortality to one-tenth but the period of hospitalization was greatly reduced. Complications from bleeding were rare with this form of treatment, there being three cases of hematuria and two patients who developed hemarthrosis. It is interesting to note that Bauer does not mention the necessity of controlling the dosage of heparin by determinations of the clotting time. It is well known that the depression of the clotting time following intravenous administration of heparin is not evenly sustained (Walker[48]) and so with this intermittent type of administration there must be periods during the 24 hours when the patient is not protected against intravenous thrombosis. On the other hand, the clinical results reported with the intermittent heparinization are so uniformly favorable that the need for continuous administration may be questioned, especially since the complicating factor of hemorrhage may be avoided by the less intensive form of treatment. Administration of heparin in Pitkin Menstruum, a form which allows it to be slowly released over a two-day period, has been developed by Loewe[33] and his associates. Favorable results with this form of treatment were reported in 125 cases, although there were four cases of fatal embolism. They advocated prolonged treatment, 10 to 14 days for uncomplicated thrombophlebitis and three to four weeks after pulmonary embolism. The need for such prolonged therapy may be questioned, especially in case that active mobilization is feasible after a short period of heparinization. The use of heparin/Pitkin in combination with dicoumarol has been advocated by Evans and Boller.[21] The two drugs are given simultaneously and the heparin effect on the clotting time wears off at just about the time that the depressant effect of the dicoumarol on the prothrombin level becomes effective.

Comment. Heparin, according to all reports, is effective in the prevention of thrombo-embolism. Its action in arresting the process of intravascular thrombosis is especially desirable. It is, however, expensive and its administration cumbersome. Control of the dosage by determinations of the clotting time is not difficult and the occurrence of complicating hemorrhage has been reported only rarely.

Dicoumarol. Dicoumarol, the hemorrhagic agent from spoiled sweet clover first isolated and synthesized by Link, prevents the formation of prothrombin in the liver. It has been extensively used in the prevention and treatment of thrombo-embolism. In 1,000 cases reported by Barker, Cromer, Hurn and Waugh[7] from the Mayo Clinic, there was but one death from pulmonary embolism and this embolism occurred after the prothrombin had returned to normal because the

Dicoumarol had been given for insufficient time. This record is the more impressive since Dicoumarol was used in 379 cases of thrombosis or embolism in which the incidence of subsequent thrombo-embolism is so high. This drug is given by mouth, 200 mgm. to patients under 150 lb. in weight and 300 mgm. in those who weigh over 150 lb. The prothrombin time must be accurately checked before the administration of any more Dicoumarol since 27 per cent of 340 consecutive patients studied by Barker and his associates were hypersensitive to the drug. In cases of hypersensitivity the prothrombin may fall to less than 10 per cent of normal after the first one or two doses or after subsequent doses. Serious bleeding may take place under these circumstances. The full effect of the administration of Dicoumarol does not occur for 24 to 48 hours and sometimes even longer. Again, the prothrombin deficiency may continue for from two to ten days after the last dose of Dicoumarol has been given. Barker and his associates recommended that the prothrombin level be kept between 10 and 30 per cent of normal by the administration of 200 mgm. of Dicoumarol on each day that the prothrombin was greater than 20 per cent of normal. In the first 497 cases in whom Dicoumarol was used postoperatively to prevent thrombo-embolism Barker, Allen and Waugh[8] reported bleeding of some degree in 47, an incidence of almost 10 per cent. In 4 per cent the bleeding was more than slight and there was one fatality. In this case the prothrombin time was only 28 seconds, so that the part played by Dicoumarol in the production of this fatal hemorrhage may be questioned. In all the remaining cases of moderately severe or severe bleeding the prothrombin time was in excess of 60 seconds. Evans,[20] in reporting on the use of Dicoumarol in 55 cases encountered hemorrhages in eight patients with two fatalities. In a recent report[21] he has reduced the dosage of Dicoumarol to 100 mgm. and this dose is given only after the prothrombin time has been found to be above 65 per cent. deTakats[18] attempts to maintain the prothrombin level between 60 and 30 per cent. Prothrombin deficiency due to the action of Dicoumarol can be effectively counteracted both by transfusions of fresh whole blood and by the intravenous administration of synthetic vitamin K in the form of Menadione bisulfite. According to Barker,[7] a single dose of 64 mgm. was sufficient in 35 of the 37 patients who were treated for this complication, to bring the prothrombin time down to a safe level. The possibility of precipitating a recurrence of thrombosis with such large doses should be kept in mind. deTakats[18] has reported two cases in whom fresh vascular accidents appeared to coincide with the administration of the vitamin.

Of great interest is the recent report by Allen[3] on the use of Dicoumarol in small dosage for the prevention of thrombo-embolism at the Massachusetts General Hospital. In a well-controlled series of 101 cases, 200 mgm. of Dicoumarol was administered to patients between the ages of 40 and 65 on the second or third day after operation. In ten patients in this series a second dose of Dicoumarol was given. There were but three instances of thrombo-embolic complications and in two of these the dosage of Dicoumarol had no appreciable effect on the prothrombin time. In the control group who "were comparable in every respect to those in the same age group receiving Dicoumarol" there were 14 instances of thrombosis requiring vein interruption. In those receiving Dicoumarol there were no undesirable sequelae which could be definitely attributed to the use of the anticoagulant. Although this series is too small for the results to be statistically significant, the observations are extremely interesting in that they suggest the possibility of administering Dicoumarol in dosage small enough not to produce the complication of hemorrhage but yet sufficient to reduce very substantially the complication of thrombo-embolism. In addition, the small dosage given may permit the routine administration of Dicoumarol without the necessity of the highly specialized determination of the prothrombin time.

Comment. There are numerous contraindications to the use of Dicoumarol: (1) hepatic or renal disease, (2) blood dyscrasias, (3) recent operations upon the brain, spinal cord and thorax in which postoperative hemorrhage may be hazardous, and (4) granulating wounds or conditions requiring drainage from the gastrointestinal tract. Again, prophylactic use of Dicoumarol is hardly feasible in patients confined to bed for prolonged periods of time because of cardiac, pulmonary or other serious medical conditions. In addition, because the individual reaction to Dicoumarol is unpredictable, this anticoagulant should not be given in large doses unless facilities are available for accurate determinations of the prothrombin level. Dicoumarol is easier to give than heparin; it is less expensive and the effect lasts longer. Complications from hemorrhage are more frequent than with the use of heparin, according to reports from the literature. Just as with heparin, thrombo-embolism may recur after discontinuation of the drug. All those who have used Dicoumarol have for it a healthy respect. Under strict control it has been a great boon, but without constant vigilance it can be a serious threat to the life of the patient.

REFERENCES

1. Allen, A. W., Linton, R. R., and Donaldson, G. A.: Thrombosis and Embolism. Review of 202 Patients Treated by Femoral Vein Interruption, Ann. Surg., 118: 728, 1943.

2. Allen, A. W., Linton, R. R., Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism; Further Experiences with Thrombectomy and Femoral Vein Interruption, J.A.M.A., 128:397, 1945.

3. Allen, A. W.: Thrombosis and Embolism; A Preliminary Report on the Comparative Results of Femoral Vein Interruption and Dicoumarol Therapy, Bull. N. Y. Acad. Med., 22:169, 1946.

4. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, W. B. Saunders Co., Philadelphia, pg. 625, 1946.

5. Bancroft, F. W.: Prozimal Ligation and Throm-

bectomy for Phlebothrombosis of the Femoral and Iliac Veins, Ann. Surg., 121:175, 1945.

6. Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. III. Time of Occurrence During the Postoperative Period, Proc. Staff Meetings of Mayo Clinic, 16:17, 1941.

7. Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M.: The Use of Dicoumarol in the Prevention of Postoperative Thrombosis and Embolism with Special Reference to Dosage and Safe Administration, Surg. 17:207, 1945.

8. Barker, N. W., Allen, E. V., and Waugh, J. M.: The Use of Dicoumarol (3,3' Methylenebis (4-Hydroxy-Coumarin)) in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, Proc. Staff Meetings Mayo Clinic, 18:102, 1943.

9. Bauer, G.: Heparin Therapy in Acute Deep Venous Thrombosis, J.A.M.A., 131:196, 1946.

10. Bauer, G.: A Roentgenological and Clinical Study of the Sequels of Thrombosis, Acta. Chir. Scand. 86 (Supp.):1, 1942.

11. Bauer, G.: Thrombosis Following Leg Injury, Acta. Chir. Scand., 90:229, 1944.

12. Blodgett, J. B., and Beattie, E. J.: Early Postoperative Rising; A Statistical Study of Hospital Complications, S. G. & O., 82:485, 1946.

13. Brambel, C. E., and Loker, F. F.: Significance of Variations of Prothrombin Activity of Dilute Plasma, Proc. Soc. Exp. Biol. & Med., 53:218, 1943.

14. Burch, G. E., and Winsor, T.: Physiological Studies on Five Patients Following Ligation of the Inferior Vena Cava, Proc. Soc. Exp. Biol. & Med., 53: 135, 1943.

15. Chapman, E. A., and Linton, R. R.: Mode of Production of Pulmonary Emboli, J.A.M.A., 129:196, 1946.

16. Crafoord, C., and Jorpes E.: Heparin As a Prophylactic Against Thrombosis J.A.M.A., 116:831, 1941.

17. Dennis, C.: Disaster Following Femoral Vein Ligation for Thrombophlebitis; Relief by Fasciotomy, Surg., 17:264, 1945.

18. deTakats, G., and Fowler, E. F.: The Problem of Thrombo-Embolism, Surg., 17: 153, 1945.

19. deTakats, G.: Heparin Tolerance; A Test of the Clotting Mechanism, S. G. & O., 77:31, 1943.

20. Evans, J. A.: Dicoumarol Thrombotic Emergencies, New England J. Med., 230:131, 1944.

21. Evans, J. A., and Boller, R. J.: The Subcutaneous Use of Heparin in Anticoagulation Therapy, J.A. M.A., 131:879, 1946.

22. Fine, J., and Starr, A.: The Surgical Therapy of Thrombosis of the Deep Veins of the Lower Extremities, Surg., 17:232, 1945.

23. Fischer, H.: Eine Neue Therapie der Phlebitis, Med. Klin. Berl., 6:1172, 1910.

24. Golodner, H., Morse, L. J., and Angrist: Pulmonary Embolism in Fractures of the Hip, Surg., 18: 418, 1945.

25. Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings with Special Reference to Pulmonary Embolism and Infarction, Am. J. Roentgen, 43:305, 1940.

26. Hampton, A. O., Prandoni, A. G., and King, J. T.: Pulmonary Embolism from Obscure Sources, Bull. Johns Hopkins Hosp., 76:245, 1945.

27. Homans, J.: Deep Quiet Venous Thrombosis in the Lower Limb. Preferred Levels for Interruption of Veins; Iliac Sector or Ligation, S. G. & O., 79:70, 1944.

28. Homans, J.: Diseases of the Veins, New England J. Med., 231:51, 1944.

29. Homans, J.: Diseases of the Veins, New England J. Med., 235:163, 1946.

30. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Leg; Its Clinical Significance As Exemplified in 351 Autopsies, Arch. Int. Med., 68:1, 1941.

31. Hunter, W. C., Krygier, J. J., Kennedy, J. C., and Sneeden, V. D.: Etiology and Prevention of Thrombosis of the Deep Leg Veins, Surg., 17:178, 1945.

32. Jensen, D. R.: The Problem of Thrombophlebitis, Ann. Surg., 121:314, 1945.

33. Loewe, L., Rosenblatt, P., and Hirsch, E.: Venous Thromboembolic Disease, J.A.M.A., 130:386, 1946.

34. Moses, W. R.: The Early Diagnosis of Phlebothrombosis, New England J. Med., 234:288, 1946.

35. Moses, W. R.: Ligation of the Inferior Vena Cava or Iliac Veins; A Report of 36 Operations, New England J. Med., 235:1, 1946.

36. Murray, G. D. W., and Best, C. H.: The Use of Heparin in Thrombosis, Ann. Surg., 108:165, 1938.

37. Naide M. and Säyen A.: A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases with Special Reference to the Etiology and Prevention of Thrombophlebitis Am. J. Med. Sc., 207:606, 1944.

38. Ochsner, A. Intravenous Clotting, Surg., 17:240, 1945.

39. Ochsner, A., and deBakey, M.: Therapy of Phlebothrombosis and Thrombophlebitis, Arch. Surg., 40:208, 1940.

40. O'Neil, E. E.: Ligation of the Inferior Vena Cava in the Prevention and Treatment of Pulmonary Embolism, New England J. Med., 232:641, 1945.

41. Papper, E. M., and Imber, A. E.: The Use of Phlebography and Lumbar Sympathetic Block in the Diagnosis of Venospasm of the Lower Extremities, Surg., 15:402, 1944.

42. Rössle, R.: Ueber Die Bedeutung und Die Enstehung der Wadenvenenthrombosen, Virch. Arch. f. path. Anat., 300:180, 1937.

43. Shapiro, S.: Hyperprothrombinemia, a Premonitory Sign of Thromboembolization, Exp. Med. & Surg., 2:103, 1944.

44. Shaw, W. F., and Richard, C. E. B.: Postoperative Exercises As a Preventive of Embolism, J. Obst. & Gynec. Brit. Emp., 45:451, 1938.

45. Snell, A. M.: The Relation of Obesity to Fatal Postoperative Pulmonary Embolism, Arhc. Surg., 15: 237, 1927.

46. Tannenberg, J.: The Role of Allergy in the Pathogenesis of Progressive Thrombosis, Arch. Path., 23:501, 1937.

47. Veal, J. R., and Hussey, H. H.: Surgery of Deep Venous Thrombosis of the Lower Extremity, Surg., 17:218, 1945.

48. Walker, J., Jr.: The Efficacy of Heparin Administered by Intravenous, Intramuscular and Subcutaneous Routes and a Study of the Effect of Five Bacteriostatic Agents on Heparin Action, Surg., 17:54, 1945.

49. Wright, H. P.: The Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anticoagulants, J. Path, & Bact., 53:255, 1941.

50. Zilliacus, H.: On the Specific Treatment of Thrombophlebitis and Pulmonary Embolism with Anticoagulants with Particular Reference to Post-thrombotic Sequelae, Acta. Med. Scand. Supp., 171, 1946.